Stereocontrolled Synthesis of (±)-Deoxypodophyllotoxin *via* the Benzyl Equivalent of the Peterson Reaction

Seiichi Takano,* Shizuo Otaki, and Kunio Ogasawara

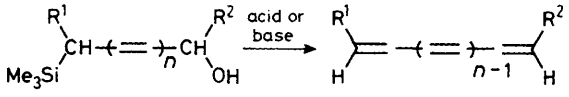
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Thermal treatment of the *o*-hydroxymethylbenzylsilane (**3**) with an excess of maleic anhydride yielded the 1,2,3-trisubstituted tetrahydronaphthalene (**8**) with a *cis* configuration, *via* the benzyl equivalent of the Peterson reaction, which was converted stereoselectively into (±)-deoxypodophyllotoxin (**13**) in good overall yield *via* a regio- and stereo-selective sequence of reactions.

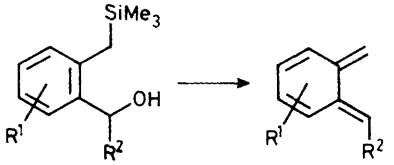
A β-hydroxysilane derivative readily undergoes elimination under both acidic and basic conditions to give an olefin.[1,2] This reaction, known as the Peterson reaction, has been found to occur in a vinylogous system giving rise to a conjugated diene under both acidic or basic conditions (equation 1).[3] The reaction has not been reported for the benzyl analogue, which would generate *o*-quinodimethane (equation 2), although fluoride catalysed *o*-quinodimethane formation by 1,4-elimination of *o*-methylammonium- or epoxy-benzylsilane derivatives is known.[4,5]

We report here the first example of an acid catalysed benzyl equivalent of the Peterson reaction which allows efficient generation of an *o*-quinodimethane species (**7**) from an *o*-hydroxymethylbenzylsilane (**3**) under weak acidic conditions without using a fluoride catalyst. The *o*-quinodimethane (**7**) thus generated was trapped *in situ* with maleic anhydride to give the adduct (**8**) which could be regio- and stereo-selectively converted into the naturally occurring antitumour lignan lactone deoxypodophyllotoxin (**13**)[6–8] in satisfactory overall yield.

Bromination of 3,4-methylenedioxybenzylsilane (**1**),[9]† b.p. 130—133 °C (20 mmHg), easily prepared from 3,4-methylenedioxybenzyl chloride, proceeded smoothly to give the 6-bromide (**2**), b.p. 100—102 °C (0.1 mmHg), in 87%

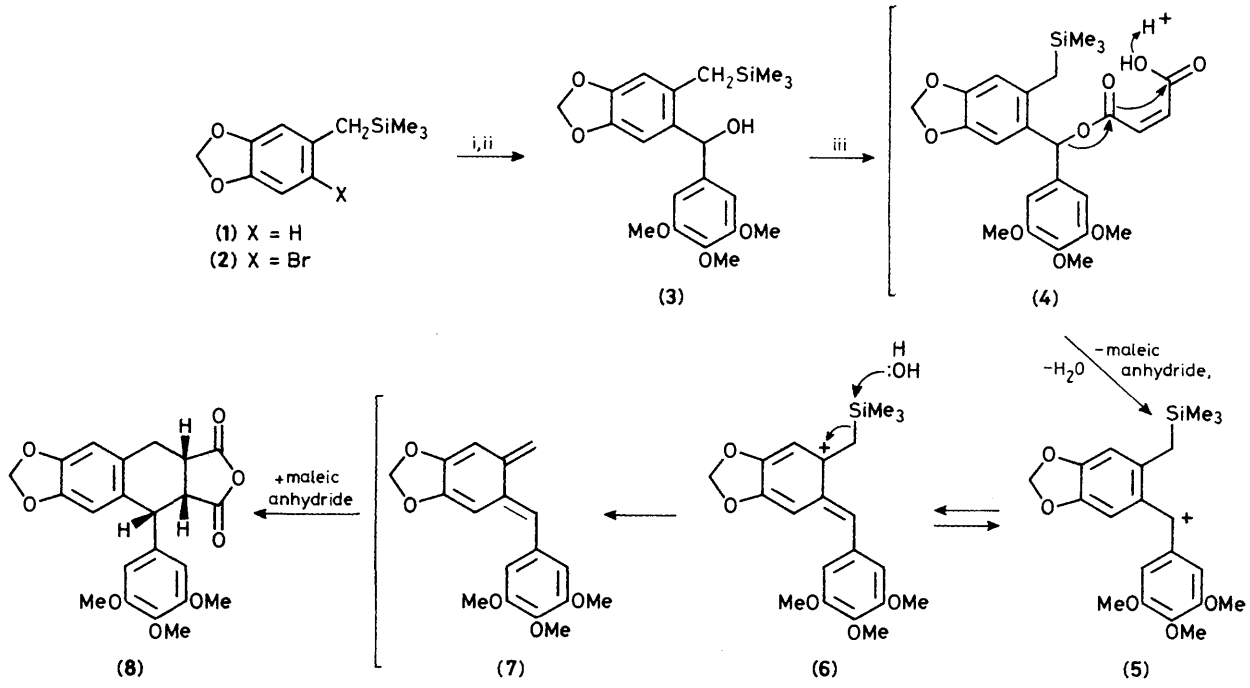


(1)

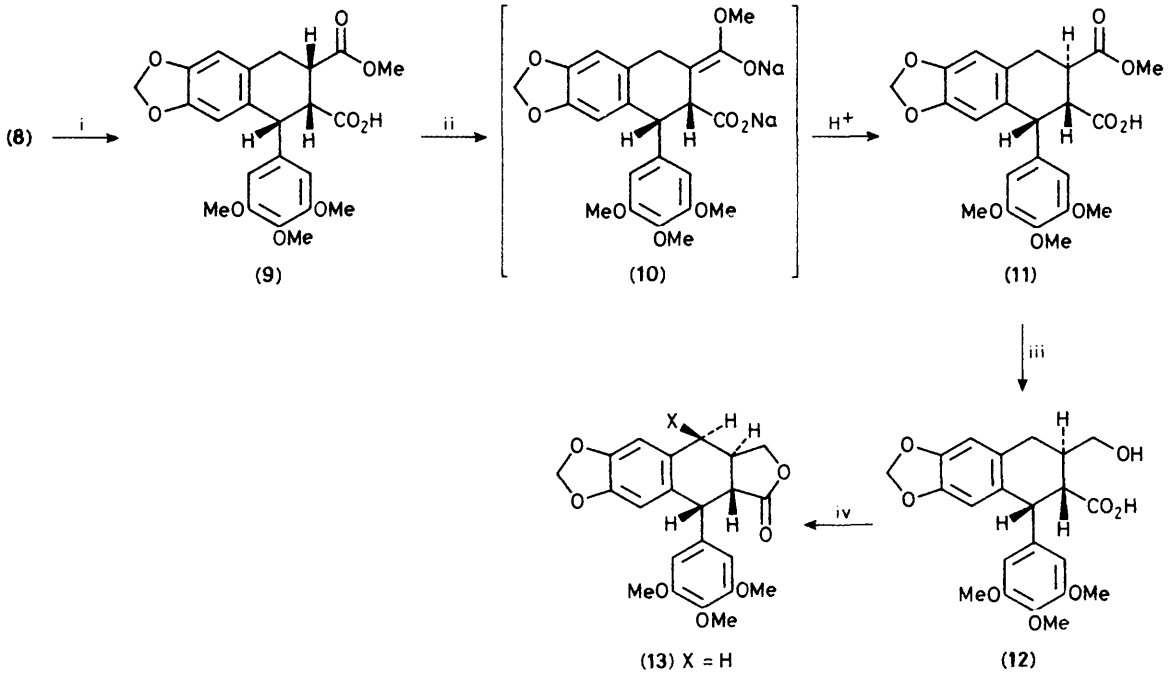


(2)

† Satisfactory elemental analyses and high resolution mass spectral data were obtained for all new compounds.



Scheme 1. *Reagents:* i, Br_2, 5% aq. $NaHCO_3$, CH_2Cl_2; ii, Bu^nLi, tetrahydrofuran (THF), −78 °C, then 3,4,5-$(MeO)_3C_6H_2CHO$; iii, maleic anhydride, toluene, reflux.



Scheme 2. *Reagents:* i, MeOH, reflux; ii, MeONa, MeOH, reflux, then acid work-up; iii, lithium triethylborohydride, THF, −20 °C, then acid work-up; iv, toluene-*p*-sulphonic acid, benzene, reflux.

yield. Treatment of (**2**) with n-butyl-lithium followed by treatment with 3,4,5-trimethoxybenzaldehyde (1 equiv.) at the same temperature afforded a 92% yield of (**3**), m.p. 95—97 °C. Heating of (**3**) at reflux with an excess (5 equiv.) of maleic anhydride in toluene (24 h) gave rise to the known *cis*-adduct (**8**),[10] m.p. 182.5—183.5 °C (lit.[10] m.p. 185 °C), in 64% yield. Virtually the same result was obtained using benzene instead of toluene although a longer reaction time (36 h) was required. We assumed that the reaction proceeded with formation of half ester (**4**), followed by elimination of maleic anhydride and water by the catalysis of the acid (**4**) itself to give the benzyl cation (**5**) equilibrated with the β-silyl cation (**6**), which in turn reacted with water or another molecule of (**4**) to generate (**7**), and finally cycloaddition between (**7**) and maleic anhydride occurred to give (**8**) in a stereoselective fashion. The adduct (**8**) gave the half ester (**9**),

m.p. 216.5—218 °C, ^{1}H n.m.r. ($CDCl_3$): δ 4.15 (1H, d, *J* 6.0 Hz, 1-H), in 96.5% yield, as a single isomer on methanolysis by regioselective reaction at the less hindered side of the anhydride moiety.

Treatment of (**9**) with sodium methoxide (2 equiv.) in refluxing methanol allowed selective epimerization at the ester carbonyl group to transform the thermodynamically less stable all-*cis*-isomer (**9**) into the more stable 1,2-*cis*-2,3-*trans*-isomer (**11**), ^{1}H n.m.r. ($CDCl_3$): δ 4.50 (1H, d, *J* 4.5 Hz, 1-H), quantitatively, *via* the sodium enolate (**10**). Reduction of (**11**) with lithium triethylborohydride[11] gave the hydroxy acid (**12**) which on reflux in benzene gave (±)-deoxypodophyllotoxin (**13**),[12] m.p. 234—236 °C (natural,[6] m.p. 167—168 °C; synthetic,[12] m.p. 236 °C) in 72% overall yield from (**11**), whose spectral (i.r., ^{1}H n.m.r., and mass) and t.l.c. behaviour were identical in all respects with those of an authentic material from natural origin.

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